

# Gastric Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

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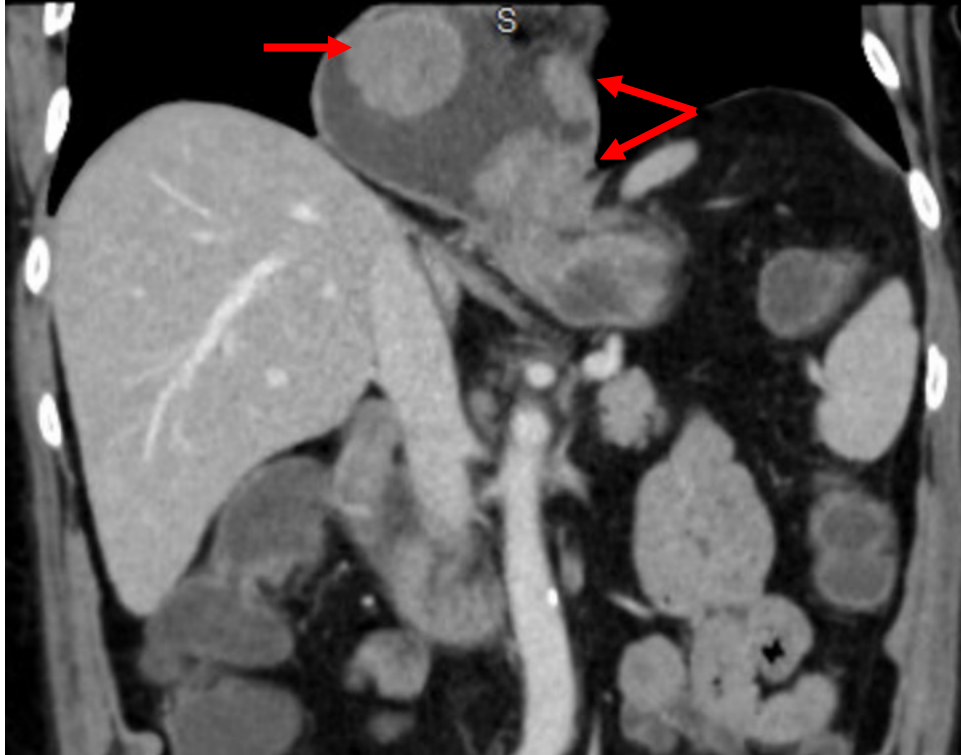
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Madison, Wisconsin

# Case#1 Presentation: 70yo female

- PMH GERD, hiatal hernia, eczema, and ulcerative colitis (UC) in her 20s, well controlled on sulfasalazine.
- Presented with asymptomatic gastric mucosal thickening found incidentally on CT of A/P as part of active surveillance for her UC.
  - Noted as a large polyp in the cardia and 2 smaller polyps in the body of the stomach

# Case#1 Presentation: 70yo female



- What's the ddx and next step in management?

# Case#1 Presentation: 70yo female

- DDX includes
  - Gastritis
  - Crohn's disease
  - Menetrier's disease
  - Adenocarcinoma
  - Lymphoma
  - Stromal tumors
  - Polyps

# MZL Introduction

- 3<sup>rd</sup> most common type of B-cell NHL (after DLBCL and follicular lymphoma)
  - MZL accounts for roughly 5-10% of NHL
  - MALT is the most common subtype of MZL, roughly 70%
    - Splenic MZL ~10%, and nodal MZL ~20% of cases.
- Infections (ie, H. pylori, HCV) and autoimmune conditions (ie, Sjögren's, Hashimoto's) are predisposing factors
  - Chronic inflammation -> immune response -> expand B-cell clones -> acquisition of mutations -> deregulated growth
- Can arise in GI tract > orbit > lung > skin
- Incidence increases with age

# Predisposing Factors in MZL

- Infections
- Autoimmune
- ? genetic predisposition

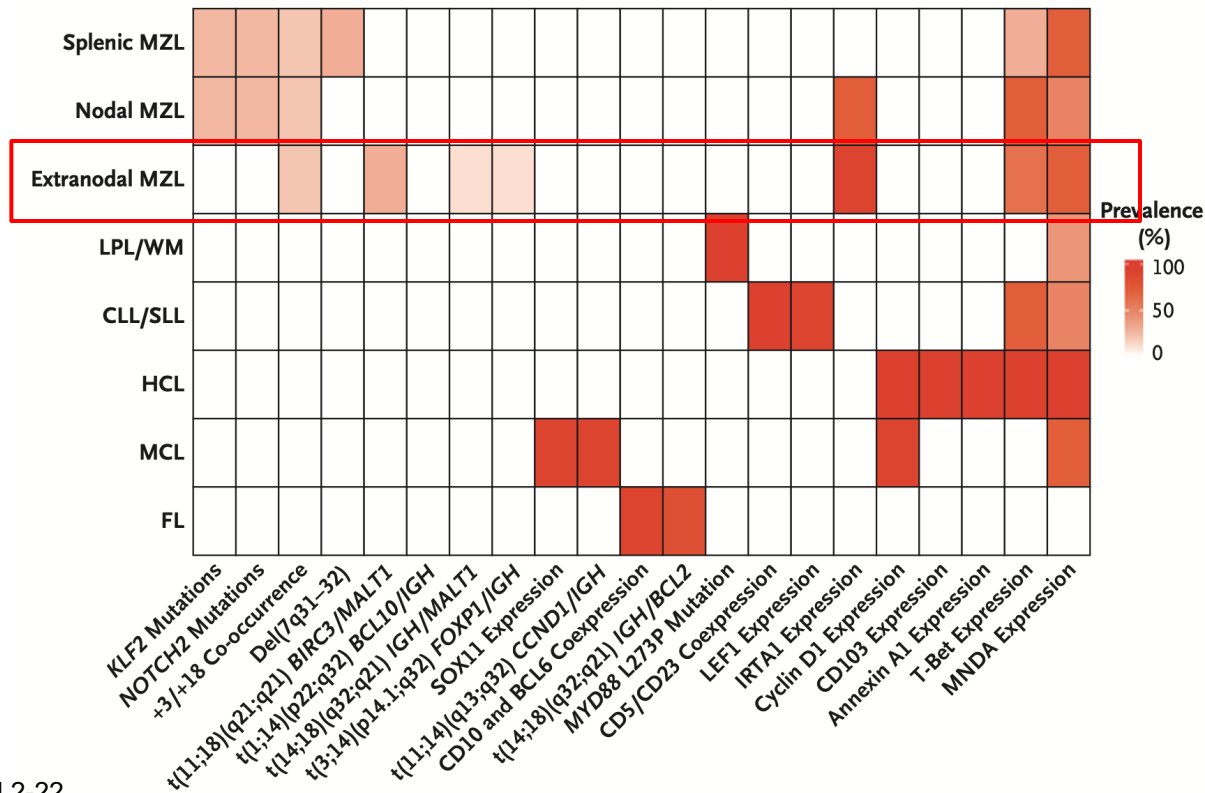
**Table 1.** Anatomical Distribution of Predisposing Conditions and Molecular Features of Marginal-Zone Lymphomas (MZLs).\*

Site of Disease	Infectious Agent	Autoimmune Condition	Biased Immunoglobulin-Gene Usage†	Recurrent Translocations	Recurrent Copy-No. Aberrations	Site-Specific Gene Mutations
Stomach	<i>Helicobacter pylori</i>	—	IGHV3–23	t(11;18)(q21;q21) <i>BIRC3/MALT1</i> t(14;18)(q32;q21) <i>IGH/MALT1</i> t(1;14)(p22;q32) <i>BCL10/IGH</i>	+3, +18	—
Ocular adnexa	<i>Chlamydia psittaci</i>	Sjögren's syndrome (in lacrimal gland MZL)	IGHV4–34	t(14;18)(q32;q21) <i>IGH/MALT1</i> t(3;14)(p14.1;q32) <i>FOXP1/IGH</i>	+3, +18	<i>TNFAIP3</i>
Lung	<i>Achromobacter xylosoxidans</i>	Lymphocytic interstitial pneumonia	—	t(11;18)(q21;q21) <i>BIRC3/MALT1</i> t(14;18)(q32;q21) <i>IGH/MALT1</i>	+3, +18	—
Intestine	<i>Campylobacter jejuni</i>	—	—	t(11;18)(q21;q21) <i>BIRC3/MALT1</i> t(1;14)(p22;q32) <i>BCL10/IGH</i>	+3, +18	—
Skin	<i>Borrelia burgdorferi</i>	—	—	t(14;18)(q32;q21) <i>IGH/MALT1</i> t(3;14)(p14.1;q32) <i>FOXP1/IGH</i>	+3, +18	—
Salivary gland	—	Sjögren's syndrome	IGHV1–69	t(14;18)(q32;q21) <i>IGH/MALT1</i>	+3, +18	<i>TBL1XR1, GPR34</i>
Thyroid	—	Hashimoto's thyroiditis	IGHV3–23	t(14;18)(q32;q21) <i>IGH/MALT1</i> t(3;14)(p14.1;q32) <i>FOXP1/IGH</i>	+3, +18	<i>TET2, TNFRSF14, CD274</i>
Lymph node	Hepatitis C virus	—	IGHV4–34	—	+3, +18	<i>KLF2, NOTCH2, PTPRD</i>
Spleen	Hepatitis C virus	—	IGHV1–2*04	t(2;7)(p11;q21) <i>IGK/CDK6</i>	+3, +18, del(7q31–32)	<i>KLF2, NOTCH2</i>

Rossi, Bertoni, Zucca NEJM 2-22

# EMZL Common Gene Alterations

- Mutational landscape & ddx of B-cell neoplasia



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# Work-up

- Complete H&P
- Labs: CBC, CMP, LDH, HepB, HepC
- Imaging: PET/CT or CT C/A/P
- Biopsy: endoscopy, not FNA
  - H. pylori testing (may not be + in ~10% of pts)
  - PCR or FISH for t(11;18)
    - Associated with locally advanced disease and tumor non-response to antibiotics
  - IHC & Flow markers
    - Typically CD5-, CD10-, CD20+, CD23-/+ , CD43 -/+ , cyclin D1-, and BCL2- follicles

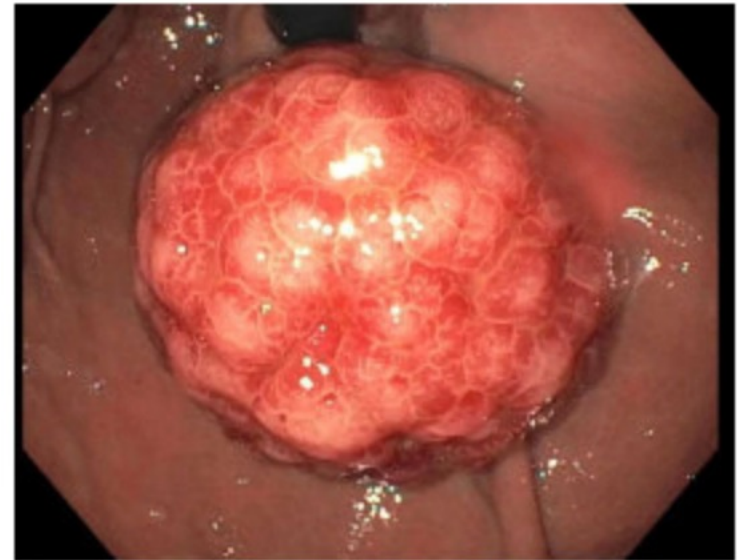


# Work-up

- Additional/other
  - Other testing for H. pylori in case negative on IHC (ie, stool antigen test or urea breath test)
  - EUS may be helpful in evaluating depth of involvement if H. pylori pos and abx planned
  - TTE if planning anthracycline-based systemic tx
  - BMBx +/- aspirate in select cases
  - Fertility preservation

# Case#1 Presentation: 70yo female

- EGD demonstrated a single, non-bleeding, semi-sessile polyp in the cardia, and 2 smaller polyps in the body.
- Colonoscopy with stable UC changes



**2** Gastric Body : Polyp(s)

# Case#1 Presentation: 70yo female

- Biopsy= extranodal marginal zone lymphoma (MZL)\* of mucosa-associated lymphoid tissue (MALT) lymphoma.
  - Dense infiltrate of small monotonous appearing CD20+ lymphocytes, negative for CD3-, CD5-, CD10-, CD21-, CD43-
  - H. pylori negative by IHC

*\*Per NCCN nongastric MALT lymphoma was recently changed to extranodal marginal zone lymphoma of nongastric site*

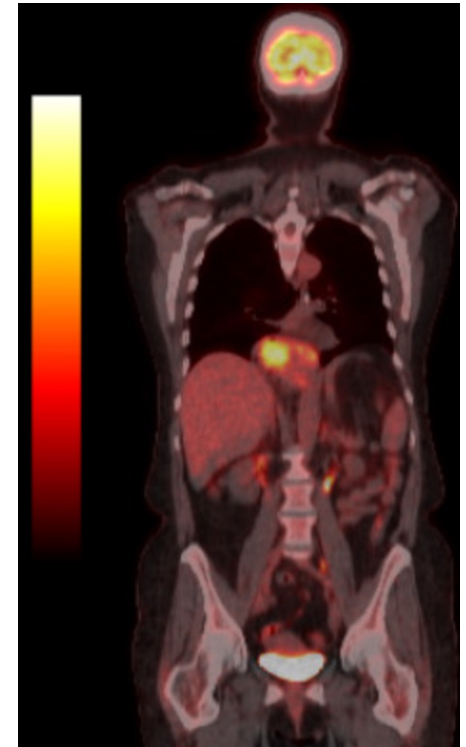
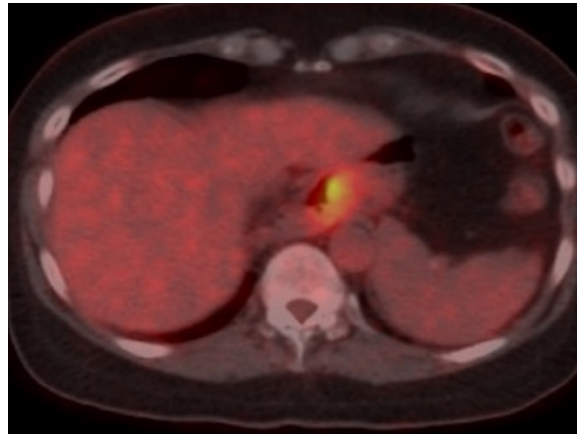
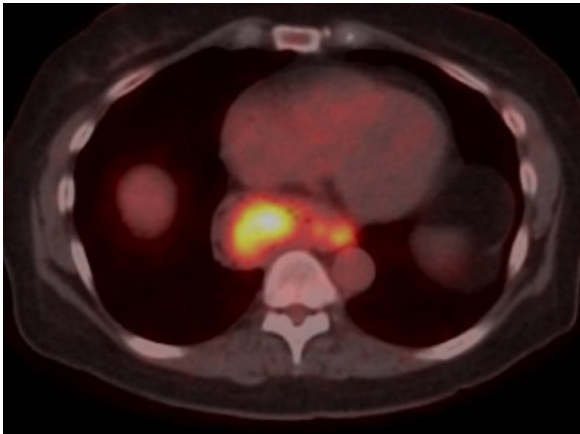
# Case#1 Presentation: 70yo female

- Labs:
  - CBC & CMP WNL; LDH mildly elevated; HepC/HepB/HIV neg
  - BMBx without lymphoma
  - H. pylori stool antigen negative

*\*Per NCCN nongastric MALT lymphoma was recently changed to extranodal marginal zone lymphoma of nongastric site*

# Case#1 Presentation: 70yo female

- PET/CT:
  - Gastric mass with SUV 10.1 measuring 7.5 x 3.2 cm with an additional component measuring 3.6 x 2.1 cm. No other disease.



- How would you stage the patient?

*\*Per NCCN nongastric MALT lymphoma was recently changed to extranodal marginal zone lymphoma of nongastric site*

# Staging

## Comparison of different staging systems

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract <sup>a</sup>			
	I <sub>1</sub> = mucosa, submucosa	I <sub>E</sub>	T1 N0 M0	Mucosa, submucosa
	I <sub>2</sub> = muscularis propria, serosa	I <sub>E</sub>	T2 N0 M0	Muscularis propria
I <sub>E</sub>		T3 N0 M0	Serosa	
Stage II	Extending into abdomen			
	II <sub>1</sub> = local nodal involvement	II <sub>E</sub>	T1-3 N1 M0	Perigastric lymph nodes
	II <sub>2</sub> = distant nodal involvement	II <sub>E</sub>	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II <sub>E</sub>	T4 N0 M0	Invasion of adjacent structures
Stage IV <sup>b</sup>	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

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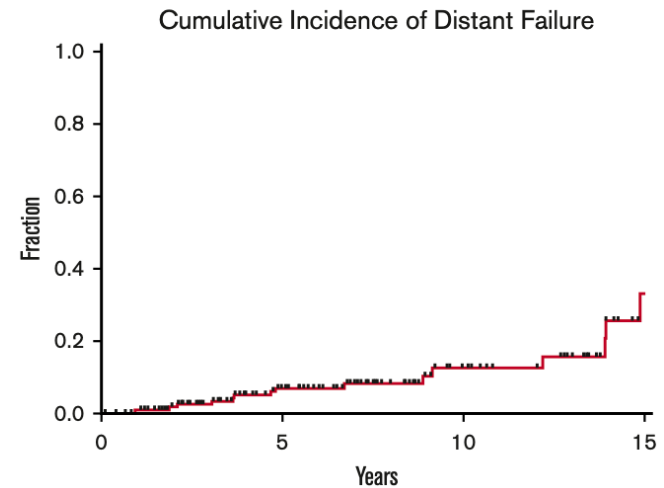
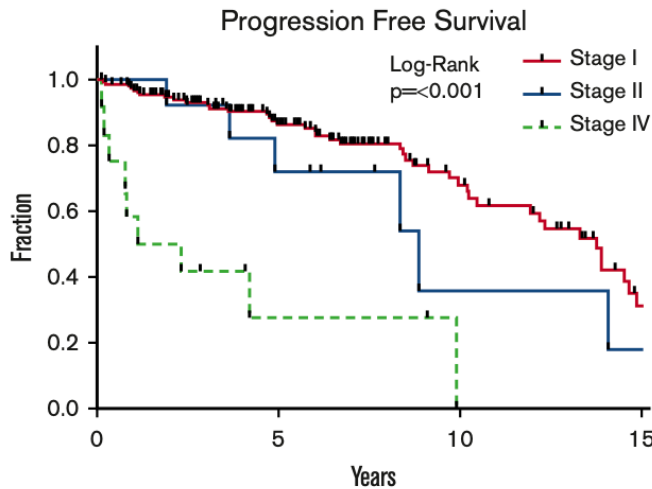
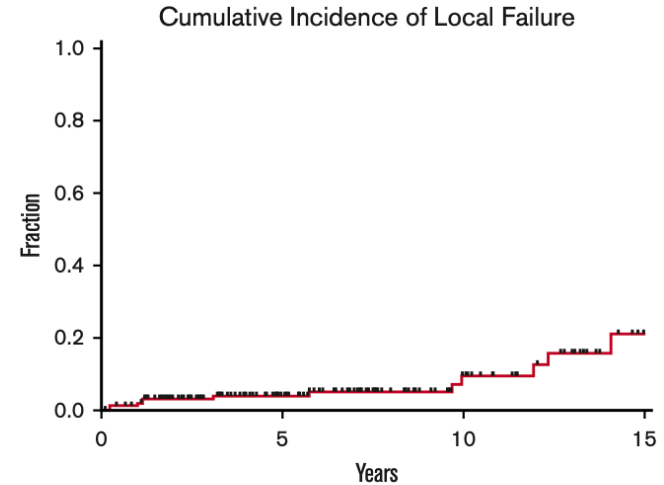
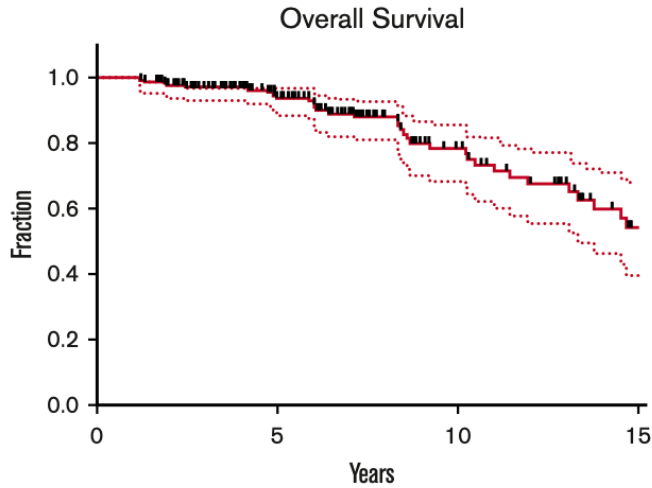
- Given a single extranodal site (gastric mass) without nodal or distant metastases, patient is staged as **stage IE disease**.
- What do you recommend for her?

# Radiation in Gastric MALT

- RR out of MSKCC 1991 – 2017
- N=178 predominately stage I (86%); stage II (7%) and IV (7%) dz
- *H. pylori* negative or persistent *H. pylori*+ s/p abx
- Median age 63y; MFU 6.2 years
- Median XRT dose 30 Gy in 1.5 Gy/F to stomach & adjacent nodes
- AEs: dyspepsia (most common); 1% rate of G3 esophageal stricture requiring dilation; 1.6% rate of in-field 2<sup>nd</sup> malignancy
- **10y outcomes include LF 10%, DF 15%, OS 80%, PFS 60%**



# Radiation in Gastric MALT



Yahalom et al; Blood Adv. 2021

July 3, 2023

# Treatment Paradigm

Stage	Setting	Treatment
I-II	H. Pylori pos; t(11;18) neg or unknown	<ul style="list-style-type: none"> <li>Antibiotics; if with persistent dz -&gt; ISRT</li> <li>If persistent H. pylori+ with PR -&gt; 2<sup>nd</sup> course of abx</li> <li>PD or symptomatic dz -&gt; ISRT + 2<sup>nd</sup> course abx</li> </ul>
	H. pylori pos; t(11;18) pos	Antibiotics and ISRT (or rituximab if XRT contraindicated)
	H. Pylori neg	ISRT (or rituximab if XRT contraindicated)
	Persistent & symptomatic dz	s/p ISRT or rituximab -> systemic therapy
IIE, II <sub>2</sub> , IV	Asymptomatic	Observation ( <i>see next slide</i> )
	Symptomatic, bulky dz, steady progression	Systemic therapy or palliative ISRT

antibiotics= triple tx (PPI, clarithromycin, amoxicillin) or quadruple tx with bismuth salicylate

# Stages II-IV Observation

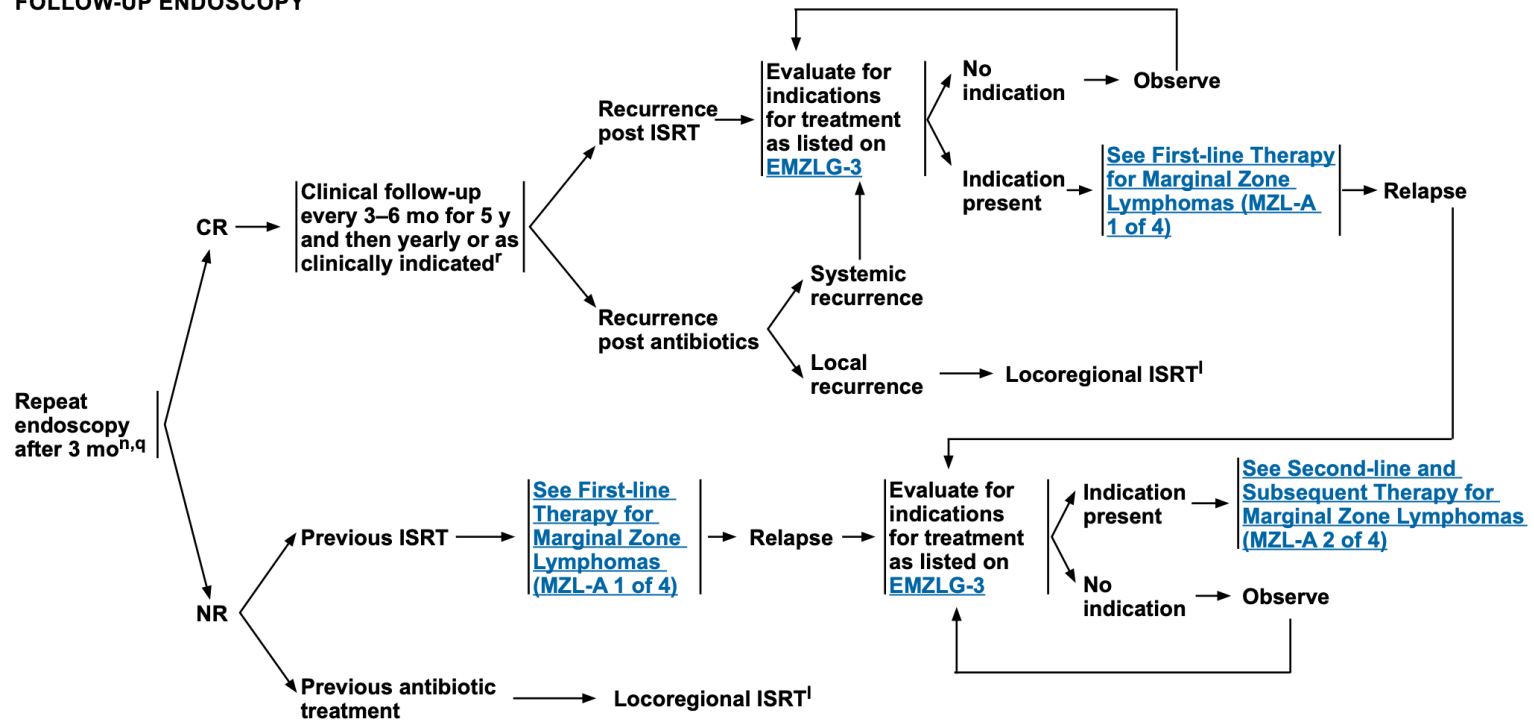
- Continuous evaluation for indications to treat. Criteria include:
  - Patient preference
  - Symptomatic disease (ie, GIB, early satiety)
  - End-organ dysfunction, ie AKI
  - Bulky disease causing symptoms
  - Persistent or rapid growth rate
- Palliative ISRT, systemic therapy, or enrollment in clinical trial (given incurability of dz) may be pursued
  - Resection limited to life-threatening symptoms (hemorrhage)
  - Total gastrectomy not recommended given significant long-term morbidity

# Few Words on Systemic Therapy

- Recommended for patients with persistent or progressive disease as noted above
  - Bendamustine + rituximab
  - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
  - CVP (cyclophosphamide, vincristine, prednisone) + rituximab
  - Rituximab (375 mg/m<sup>2</sup> weekly for 4 doses)
- For elderly patients or poor KPS
  - Rituximab (375 mg/m<sup>2</sup> weekly for 4 doses)
  - Chlorambucil +/- rituximab
  - Cyclophosphamide +/- rituximab

# Follow-up Management

## FOLLOW-UP ENDOSCOPY



<sup>l</sup> See Principles of Radiation Therapy (NHODG-D).

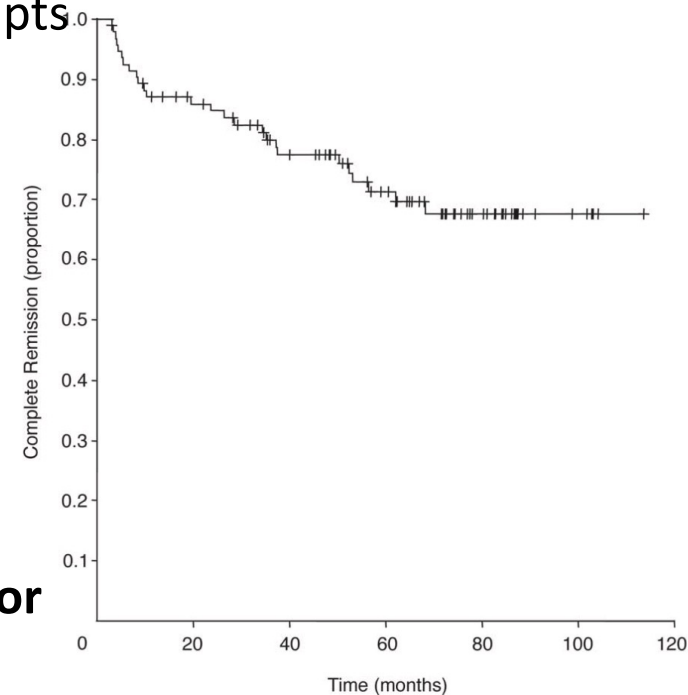
<sup>n</sup> If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. Complete responses may be observed as early as 3 months after antibiotic treatment but can take longer to achieve (up to 18 months) (category 2B).

<sup>q</sup> Reassessment to rule out *H. pylori* by institutional standards. Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated as DLCL (BCEL-1).

<sup>r</sup> Optimal interval for follow-up endoscopy and imaging is not known. At NCCN Member Institutions, follow-up endoscopy and imaging using the modalities performed during workup is driven by symptoms.

# Role for Antibiotics?

- Indicated for patients with H. pylori mediated dz (histopath and/or stool PCR) – **not our pt**
- Prospective German single-arm study of n=120 pts with stage I<sub>1E</sub> disease
- Tx:
  - 1<sup>st</sup> line: PPI, amoxicillin
  - 2<sup>nd</sup> line: PPI, flagyl, clarithromycin
- MFU 75 months
- **5y OS 90%**
- **Histologic CR 80%**
- **t(11;18) associated with higher risk of relapse or no response**

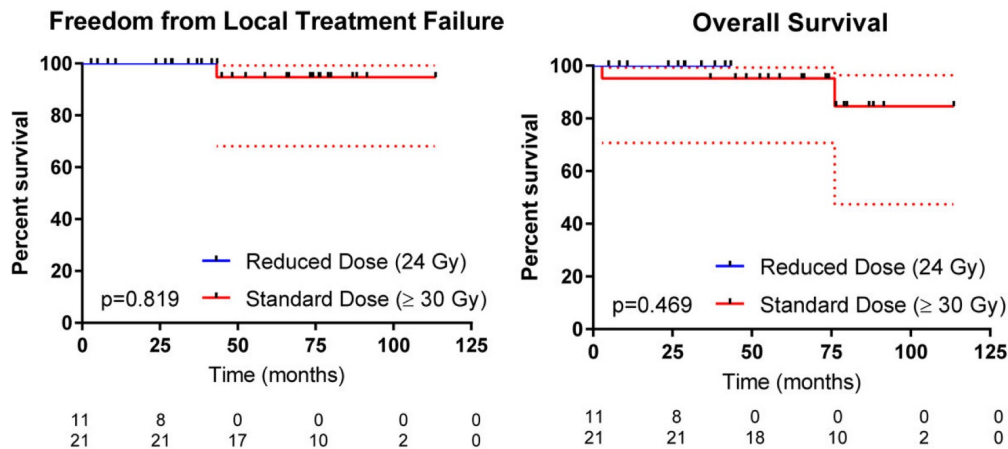


# Radiation Dose

- ISRT= 24 to 30 Gy in 1.5 Gy per fraction, both definitive and salvage, given high radiosensitivity
  - Dose-reduction per MDACC series (see next slide)
  - Ongoing trials evaluating lower dosing
- Palliative= 2 Gy x 2 fractions or 4 Gy x 1 fraction, may be repeated up to 30 Gy

# Radiation Dose Reduction

- Small series of n=32 pts with gastric MALT out of MDACC
- Median dose 30 Gy (n=21) and 24 Gy (n=11); MFU 55 mos
- **Post-RT bx with CR in all patient**
- **2y OS 97%, FFLTF 100%**
- **Small sample size for meaningful conclusions though lower dose was not associated with treatment failure**





# Current Clinical Trials

- 4 Gy in 2 fractions, phase 1 trial MDACC.
  - Assessing complete gastric response at 1-year post-tx.
- n=24; completed accrual early 2023, data is maturing.
- H. pylori testing must be negative within 6 mos prior to tx.
- Pts excluded if have DLBCL, follicular lymphoma, CLL/SLL, bulky dz >10 cm in any dimension.

# Current Clinical Trials

- 20 Gy in 10 fractions, phase 2 single-arm non-inferiority trial (compared to 30 Gy ISRT) out of Germany.
  - Assessing 6-month treatment response.
- n=83; currently accruing.
- Including pts with either MZL or FL, stages I-II localized to stomach or duodenum.
- H. pylori negative or abx resistant.
- Pts excluded if have prior GI RT, stage III-IV, HIV+, acute HBV/HCV infection, IBD.

# Treatment Planning

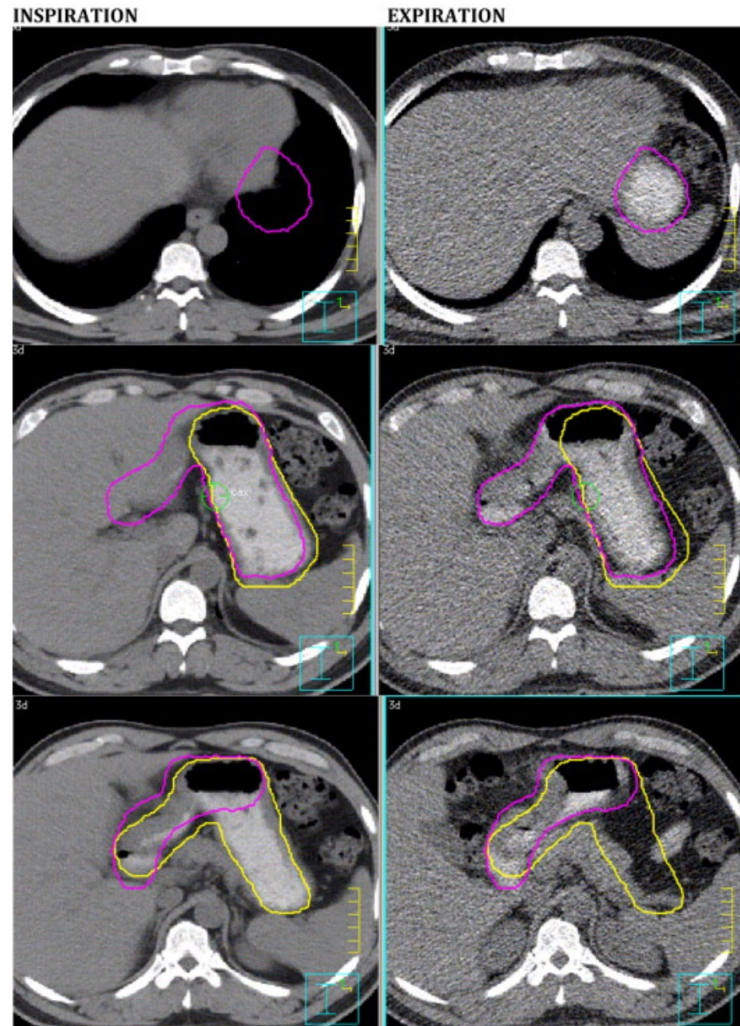
- Sim
  - Supine, arms up, mold
  - NPO 4-6 hours to minimize gastric distention/size
  - Small amount of oral contrast to help delineate target
    - If used, image before & after contrast to account for stomach distension
  - 4DCT or DIBH to account for/minimize movement of stomach
- 3D (AP/PA or 4 fields) or IMRT, using CT or MR
  - NPO 4-6 hours prior to RT
  - Anti-emetic 30-60 minutes prior to RT

# ISRT Radiation Volumes

- GTV= pre-bx gross dz
- CTV= GTV + stomach from GEJ to beyond duodenal bulb, including wall
  - Entire organ is included, lymphoma is often multifocal
  - No elective nodal irradiation; may include perigastric nodes if visible
- ITV= determined by 4DCT
  - If no 4DCT performed, add 1-2cm to CTV to account for movement
- PTV= CTV or ITV + 0.5-1 cm

# Radiation Volumes

- Example contour
  - Pink= CTVinspiration
  - Yellow= CTVexpiration
- Contouring atlas
  - Yahalom et. al, IJROBP 2015
  - eContour cases



# Constraints

- ILROG guideline (Wirth et al IJROBP 2020)

**Table 1** Dose and volume considerations

	Optimal*	Acceptable <sup>†</sup>	If necessary <sup>‡</sup>	Avoid
<b>Heart (89, 145, 146)</b>				
Mean (Gy)	<5	5-10	10-18	Coronary arteries and left ventricle
V15	<10%	10%-25%	25%-35%	
V30		<15%	15%-20%	
<b>Lung (147)</b>				
V5	<35%	35%-45%	45%-55%	
V20	<20%	20%-28%	28%-35%	
Mean (Gy)	<8	8-12	12-15	
<b>Thyroid (148)</b>				
V25	<62.5%			Whole thyroid
<b>Breast</b>				
Mean (Gy)	<4	4-15	>15	Glandular tissue
V4	<10%	10%-20%	>20%	
V10		<10%	>10%	

\* For favorable disease, small-volume early stage lymphoma.

<sup>†</sup> For bulky mediastinal disease.

<sup>‡</sup> Relapse/refractory disease setting. Adapted with permission from Dabaja et al.<sup>49</sup>

# Constraints

- NCCN Hodgkin Lymphoma also provides a general set of tissue constraints

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Abdomen	Liver	Mean <15 Gy V20 <30% V30 <20%	Hepatic toxicity <sup>34, 35</sup>
	Stomach	Dmax <45 Gy	Ulceration <sup>36</sup>
	Spleen	Mean <10 Gy V5 ≤30% V15 ≤20%	Late infections <sup>37</sup> Lymphopenia <sup>38</sup>
	Pancreas	Minimize volume >36 Gy (especially to pancreatic tail)	Diabetes <sup>39</sup>
	Small bowel	V15 <120 cc Dmax <45 Gy	Diarrhea <sup>36</sup> Obstruction, ulceration, fistula <sup>36</sup>
	Kidneys	Mean <8 Gy V10 <30% V20 <15% (recommended); <25% (acceptable)	Renal insufficiency <sup>40, 41</sup>
Other	Bone marrow <sup>e</sup>	V5: ALARA <sup>c</sup> V10 <50% V25 <25%	Acute cytopenias <sup>42,43</sup> Chronic cytopenias <sup>44</sup>
	Long bone	V40 <64%	Fracture <sup>45</sup>

## SECONDARY MALIGNANCIES<sup>f</sup>

OAR	Dose Recommendation (1.8–2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy (ideally <10%)	Breast cancer (adenocarcinoma) <sup>46</sup>
Esophagus	Minimize volume >30 Gy	Esophageal cancer <sup>47</sup>
Stomach	Minimize volume >25 Gy	Gastric cancer <sup>48</sup>
Pancreas	Minimize volume >5–10 Gy	Pancreatic cancer <sup>49</sup>

Hodgkin Lymphoma (Age ≥18 years), NCCN Guidelines Version 2.2023, 11/08/22

# Back to our 70yo patient...

- Definitive ISRT of 30 Gy in 20 fractions was recommended with MIBH delivered using MR-guided LINAC
  - MRgRT due to hiatal hernia to minimize volume and allow for adaptive planning if needed.
- Potential RT-related effects
  - Acute: fatigue, nausea, dermatitis, esophagitis, diarrhea.
  - Subacute/Late: Gastric ulceration, renal dysfunction, heart disease, pneumonitis, and secondary malignancy.



# Back to our 70yo patient...

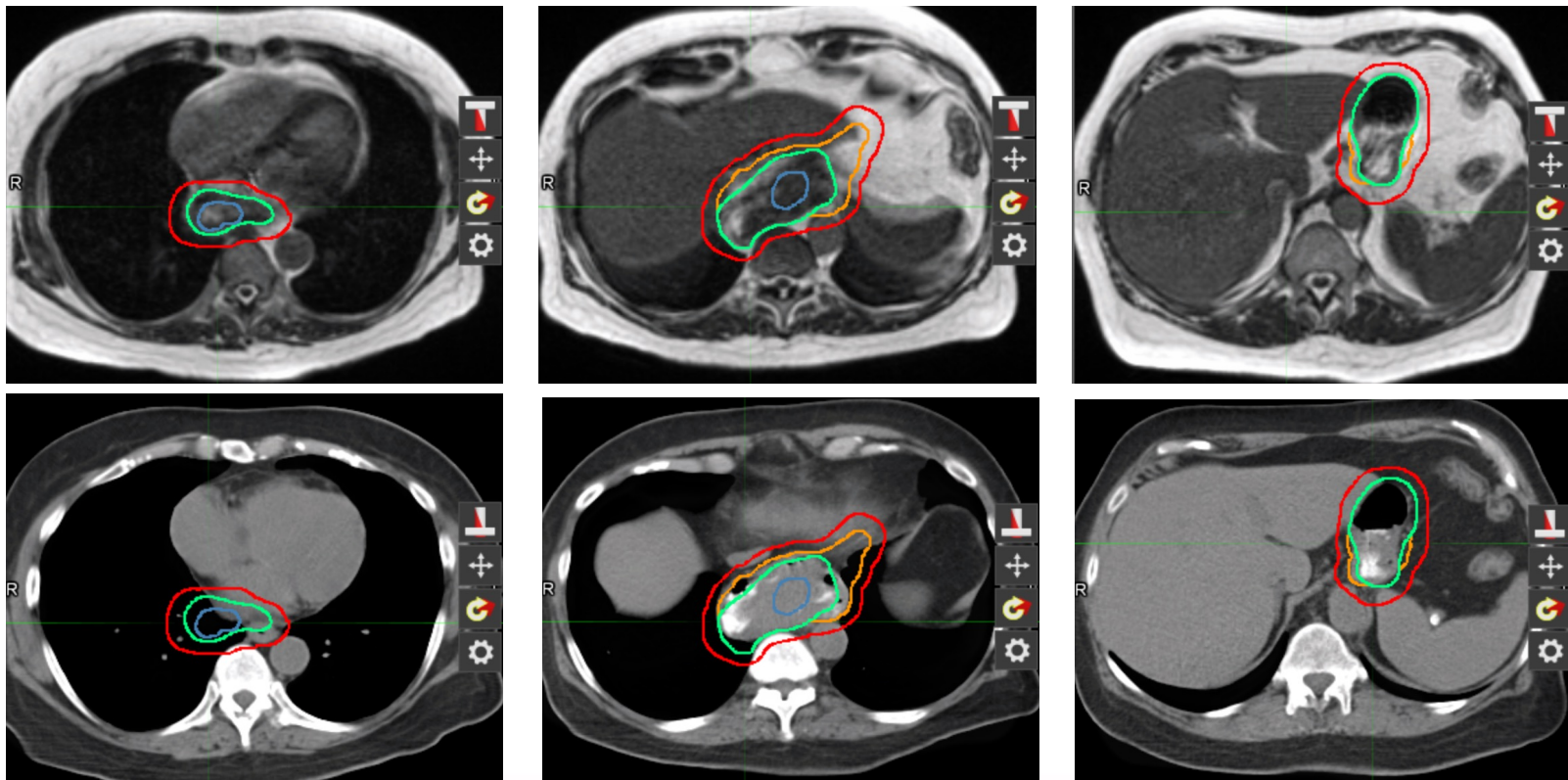
- Prescription & constraints
  - PTV\_p: D95%  $\geq$  99% Rx PTV\_p
  - Bowel: Dmax <33 Gy
  - Heart\*: Mean <7 Gy
  - Kidneys: V18 <33%
  - Kidney L/R: mean <7 Gy
  - Liver-GTV: >700cc <15 Gy
  - Spinal cord: D0.5cc  $\leq$  35 Gy
  - Lungs\*: Mean <7 Gy

*\* Heart & lung constraints are higher than typical for gastric MALT given hiatal hernia and partial intrathoracic location of stomach & GTV.*

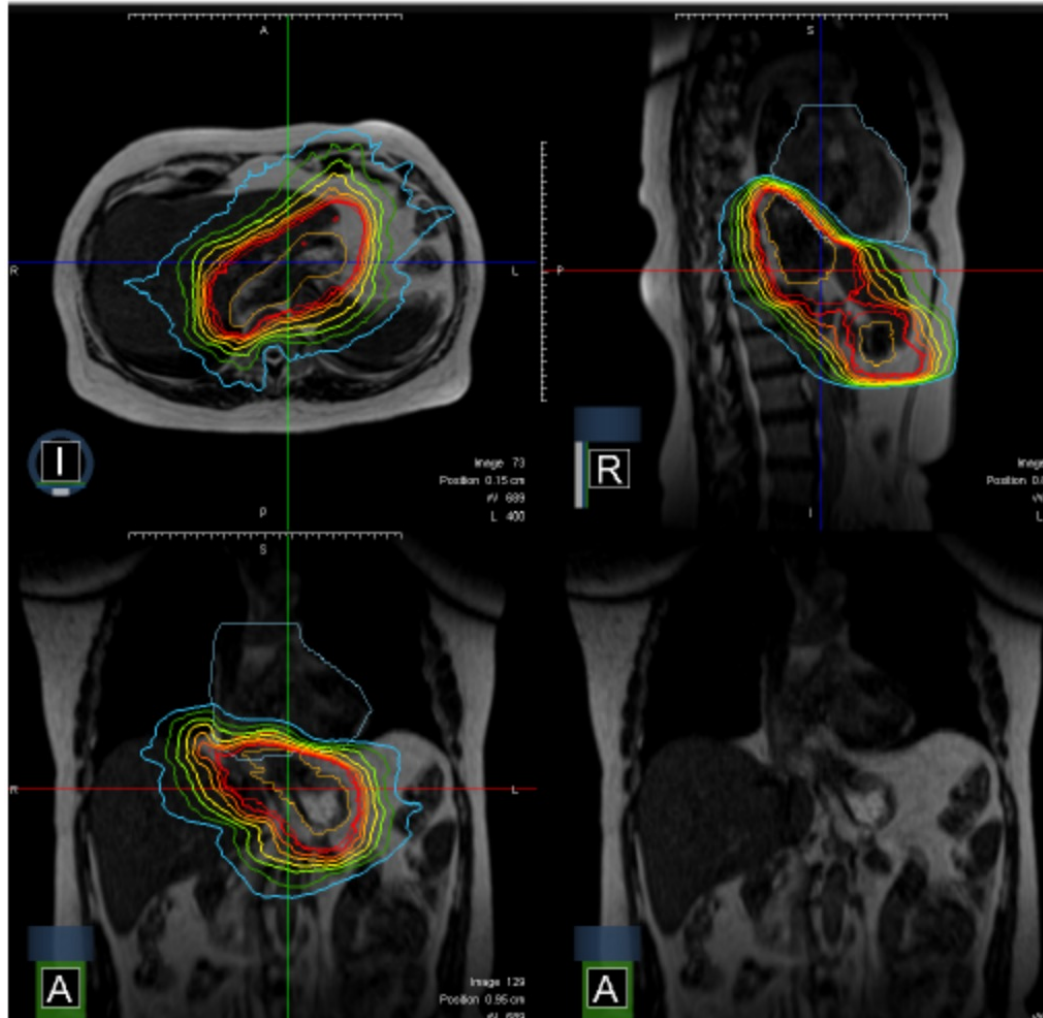
# Target Delineation



- ITV= change in position between CT and MR simulation scans



# Treatment Plan\*



## Isodose Lines

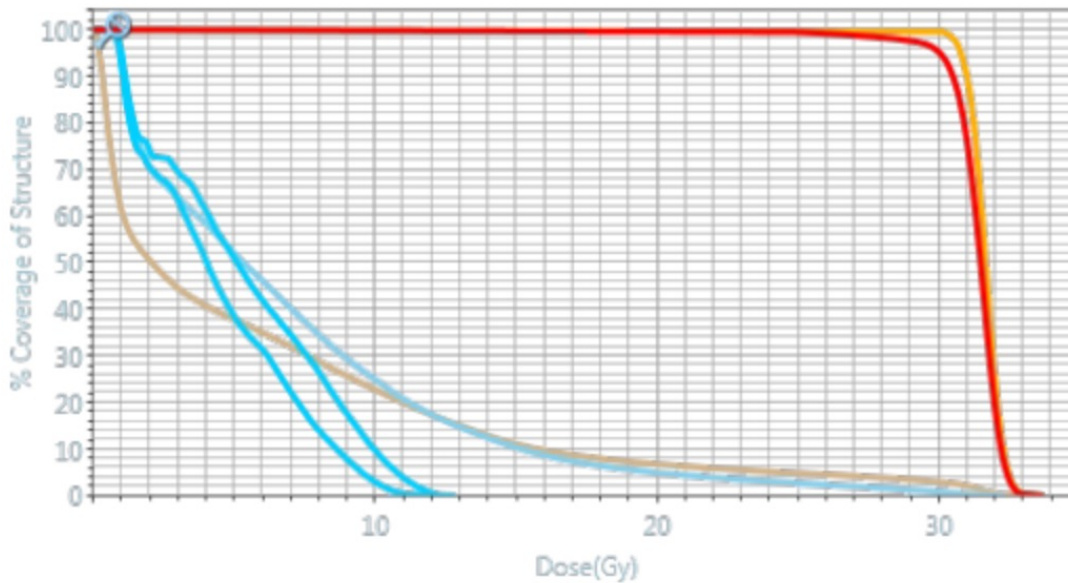
Rx Dose = 30.00 Gy

Dose (Gy)	Rx (%)
33.00	110.0
30.00	100.0
28.50	95.0
27.00	90.0
24.00	80.0
21.00	70.0
18.00	60.0
15.00	50.0

*\* Adapt treatment daily if stomach moved outside of the 24 Gy IDL (not 30 Gy)*

# Treatment Plan

DVH



Structures

Skin	Kidneys
Bowel_Large	Lungs
Bowel_Small	PTVexp
CTV_stomach	Ring_3cm
Duodenum	Normal
Esophagus	OAR_Available
GTV_PET	OAR_Rigid
Heart	Override_Tissue
ITV_stomach	Override_Air
Kidney_L	Tracking
Kidney_R	Boundary
Liver	
Lung_L	
Lung_R	
PTV_stomach	
SpinalCord	

# Follow-up

- Typically, q3-6m for 5y then annually or no FU
  - Note minimum time to CR is roughly 6 months, and typically can take twice as long
- EGD 3m post-tx with biopsy, q3-6m until resolution, then annually
  - Sooner than 3m post-tx if symptomatic/there's concern
- As for our patient, she had CR following XRT with no evidence of MALT on biopsy

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# Thank you!

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